SUDDEN CARDIAC DEATH

EPIEMIOLOGY, PATHOPHYSIOLOGY, PREVENTION & THERAPY

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SUDDEN CARDIAC DEATH (SCD)

DEATH DUE TO A CARDIAC CAUSE IN A CLINICALLY STABLE PATIENT, WITH OR WITHOUT PRE-EXISTING HEART DISEASE, WITHIN A PERIOD OF UP TO ONE HOUR AFTER AN ABRUPT AND DRASTIC CHANGE IN CLINICAL STATUS

EPIDEMIOLOGIST’S VIEW

ANNUAL DEATHS IN U.S.A

SCD CVA Lung Breast Auto AIDS Fires

EPIDEMIOLOGIST’S VIEW

MECHANISMS OF SCD

CAUSES OF SCD

- CARDIAC ARRHYTHMIA
  - Ventricular tachycardia/fibrillation
  - Asystole without an escape rhythm

- ELECTROMECHANICAL DISSOCIAION
  - Massive myocardial infarction
  - Pericardial tamponade
PATHOPHYSIOLOGY OF VT/VF

Ionic Currents during the Action Potential

Early Afterdepolarizations

(1) action potential prolongation
(2) marked action potential prolongation during terminal repolarization
(3) triggered activity

Early Afterdepolarizations Initiating VT

Reentrant Activation Initiating VT/VF

Factors Promoting Re-entrant Arrhythmias

Decreased conduction velocity
  - Partially depolarized tissue with inactivated sodium channels; myocardial ischemia
  - Scarring, disruption of architecture; chronic MI, cardiomyopathies
  - Remodeling/redistribution of connexin; ischemic heart disease, cardiomyopathies, CHF

Heterogenous refractoriness
  - Myocardial ischemia/infarction
  - Inflammation
  - Cardiomyopathies
  - Electrolyte abnormalities/drugs

DISEASES & CONDITIONS PREDISPOSING TO SCD

STRUCTURAL HEART DISEASE: ACQUIRED
A) Acute myocardial infarction
B) Chronic ischemic heart disease
C) Hypertensive heart disease
D) Dilated non-ischemic cardiomyopathy
E) Mixed dilated and hypertrophic disease: valvar
F) Infiltrative cardiomyopathy
G) Cardiac sarcoidosis

STRUCTURAL HEART DISEASE: CONGENITAL
A) Hypertrophic cardiomyopathies
B) Congenital dilated cardiomyopathies
C) Arrhythmogenic right ventricular dysplasia/CMs
D) Anomalous coronary arteries
E) Adult congenital heart diseases
F) Mitral valve prolapse

CHANNELOPATHIES/PRIMARY ELECTRICAL DISTURBANCES
A) Long QT syndromes
B) Brugada syndrome
C) Wolff-Parkinson-White syndrome
D) Familial catecholaminergic polymorphic VT
E) Short QT syndrome
F) Other repolarization abnormalities

REVERSIBLE CONDITIONS
A) Myocardial ischemia
B) Severe electrolyte imbalance
C) Acquired long QT syndrome
D) Other proarhythmic effects of drugs
E) Interactions with genetic polymorphisms
ACUTE CORONARY THROMBOSIS

VF during STEMI

CHRONIC ISCHEMIC HEART DISEASE

VENTRICULAR TACHYCARDIA IN A PATIENT WITH CHRONIC MI

Hypertrophic Cardiomyopathy

ARRHYTHMOGENIC RV DYSPLASIA
Genetic Loci Responsible for Long QT Syndrome

### GENES IDENTIFIED TO DATE IN LQT SYNDROME

<table>
<thead>
<tr>
<th>Loci</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Frequency</th>
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<tr>
<td>LQT1</td>
<td>17p11</td>
<td>KCNQ1</td>
<td>50%</td>
</tr>
<tr>
<td>LQT2</td>
<td>7q31</td>
<td>KCNE1</td>
<td>20%–40%</td>
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<tr>
<td>LQT3</td>
<td>2q31</td>
<td>KCNE2</td>
<td>50%–60%</td>
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<tr>
<td>LQT4</td>
<td>4q22</td>
<td>ANKR</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT5</td>
<td>20q12</td>
<td>ANKR</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT6</td>
<td>17</td>
<td>KCNQ1</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT7</td>
<td>20q13</td>
<td>KCNQ1</td>
<td>Rare</td>
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<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene (historical name)</th>
<th>Protein</th>
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<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1 (KVLQT1)</td>
<td>β1K channel α subunit</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNE1 (HERG)</td>
<td>β1K channel α subunit</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>β1K channel α subunit</td>
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<td>LQT4</td>
<td>ANKR</td>
<td>Ankyrin-B</td>
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<tr>
<td>LQT5</td>
<td>KCNE2 (minK)</td>
<td>β1K channel β subunit</td>
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<tr>
<td>LQT6</td>
<td>ANK2</td>
<td>β1K channel β subunit</td>
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<tr>
<td>LQT7</td>
<td>KCNQ1</td>
<td>Cα1.2 Calcium channel α subunit</td>
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<td>LQT8</td>
<td>CACNA1</td>
<td>Cα1.2 Calcium channel α subunit</td>
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**ECG in Long QT Syndrome**

**LQTS and Torsades de Pointes**

**PROSPECTIVE LONGITUDINAL F/U IN LQTS**

Moss et al, Circulation 1991;84:1136
LONG-TERM FOLLOW-UP IN LQTS

- 328 PROBANDS PRESENTING WITH SYNCOPE
- 1692 FAMILY MEMBERS

LQTS-RELATED DEATH 0.9% PER YEAR IN PROBANDS, HIGHER THAN BOTH AFFECTED AND UNAFFECTED FAMILY MEMBERS

3 RISK FACTORS IDENTIFIED FOR TOTAL GROUP WITH F/U (N=1496, 72 EVENTS)
- QT DURATION
- CARDIAC EVENT AT PRESENTATION
- RESTING HEART RATE

Moss et al. Circulation 1991; 84: 1139-1144

Risk Stratification in the Long QT Syndrome

Risk Stratification in Long QT Syndrome:
Genotype & Gender

BRUGADA SYNDROME

Natural History of Brugada Syndrome
Risk Stratification in Brugada Syndrome

Risk Groups
- Higher Risk
- Intermediate Risk
- Lower Risk

Percentage of Population
- 10% anormal and spontaneous ECG pattern
- 41% spontaneous ECG pattern
- 49% negative baseline ECG with or without syncope

PRE-EXCITED QRS COMPLEXES IN A PATIENT WITH WPW SYNDROME

SHORT QT SYNDROME

Familial catecholaminergic polymorphic VT

Mutations in the Cardiac Ryanodine Receptor Gene (RyR2) Underlie Catecholaminergic Polymorphic Ventricular Tachycardia

In the context of clinical can be divided into two pathways: 1. Dominant negative RyR2 mutations lead to increased 

Familial catecholaminergic polymorphic VT

Familial catecholaminergic polymorphic VT
Familial catecholaminergic polymorphic VT: Bidirectional VT in a Child

MAJOR ARRHYTHMIC EVENTS DURING F/U IN IDIOPATHIC VF

ACQUIRED LONG QT
ION CHANNEL FOR Ik

Drug-related Repolarization Abnormality

CAUSES OF ACQUIRED LONG QT

SCD
DETECTION OF RISK

- Drugs
  - Drugs that frequently cause torsades de pointes:
    - Disopyramide
    - Quinidine
    - Sotalol
  - Other drugs with torsades de pointes at low incidence:
    - Antiarrhythmics
    - Antineoplastics
    - Ergot alkaloids
    - Macrolides
    - Ticlopidine
    - Methotrexate
  - Heart block
  - Hypokalemia, hypomagnesemia
  - Acute myocardial infarction
  - Sudden death, cerebrovascular accident
  - Cardiac transplantation

- Drug-related repolarization abnormality
  - HERG block
  - Increased action potential duration, EADs, and heterogeneity of repolarization
  - QT prolongetion
  - Torsades de pointes degenerating to VF

- Detection of risk

- Familial catecholaminergic polymorphic VT
- Bidirectional VT in a Child

- Major arrhythmic events during follow-up in idiopathic VF

- Acquired long QT
  - Ion channel for Ik

- Causes of acquired long QT

- SCD
  - Detection of risk
RISK STRATIFICATION AND UNDERLYING HEART DISEASE

AVAILABLE TESTING METHODS/PREDICTIVE MARKERS

INVASIVE
- Programmed Cardiac Stimulation (PCS)

NON-INVASIVE
- Ventricular Systolic Function (Echocardiogram, MUGA Scan, MRI)
- Ambulatory Cardiac Rhythm Monitoring for VEA/NSVT
- T-Wave Alternans
- Exercise Testing
- HR Variability
- Baroreflex Sensitivity
- QT Dispersion
- SAECG
- Genetic Markers

LARGE NUMBERS OF PATIENTS AT RISK

- Need simple, inexpensive, non-invasive diagnostic tests with high clinical accuracy
  - Sensitivity: percentage of patients with the disease identified by the test. Need screening tests with high sensitivity not to miss any patients at high risk.
  - Positive predictive accuracy (ppa): percentage of patients with a positive test that will go on to have an event. Need screening tests with high ppa to minimize unnecessary treatment with expensive therapies in patients not at high risk.

LEFT VENTRICULAR DYSFUNCTION, VEA & SURVIVAL AFTER MI

J. Thomas Bigger, Jr. Am J Cardiol 1986;57:8B

LV FUNCTION AS PREDICTOR OF SCD

GISSI-2 SURVIVAL

Non-sustained VT, Sustained VT, and VF during Holter Monitor Recording
Better Non-Invasive Risk Predictors Needed

Example: in post MI patients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Source</th>
<th>Sens</th>
<th>PPV</th>
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<tr>
<td>LVEF &lt; 0.4</td>
<td>Pedretti, 1993</td>
<td>79%</td>
<td>26%</td>
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<tr>
<td>LVEF &lt; 0.4</td>
<td>Bourke, 1991</td>
<td>73%</td>
<td>6%</td>
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<td>LVEF &lt; 0.4</td>
<td>Farrell, 1991</td>
<td>48%</td>
<td>10%</td>
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<td>SAECG</td>
<td>Pedretti, 1993</td>
<td>79%</td>
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<tr>
<td>SAECG</td>
<td>Farrell, 1991</td>
<td>64%</td>
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<tr>
<td>HRV</td>
<td>Pedretti, 1993</td>
<td>89%</td>
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<tr>
<td>HRV</td>
<td>Farrell, 1991</td>
<td>92%</td>
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<tr>
<td>HRV</td>
<td>Bigger, 1996</td>
<td>80%</td>
<td>20%</td>
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<tr>
<td>NSVT</td>
<td>Pedretti, 1993</td>
<td>42%</td>
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<tr>
<td>NSVT</td>
<td>Farrell, 1991</td>
<td>56%</td>
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PROGRAMMED CARDIAC STIMULATION (PCS):

Introducing one or more timed, premature, paced ventricular beats, via electrode-catheters placed percutaneously inside the heart, in an effort to reproduce clinical VT in the Cardiac EP Laboratory.

PCS: Limitations

- Sensitivity of PCS in ischaemic heart disease is acceptable, but its PPA is poor.
- In non-ischaemic CM, there is up to 40% incidence of clinical arrhythmic events in “non-inducible” group.
- There are no reproducible data to justify its clinical utility in HCM.
- Not even applicable in “channelopathies”.

T-Wave Alternans

Spectral Method Detects Microvolt T Wave Alternans

Alternans-Induced VT
**MGH / MIT Results**

Arrhythmia Free Survival

![Graph showing arrhythmia-free survival percentages over months for Alternans Test and EP Study.](image)

**Frankfurt CHF Study Results**

107 consecutive patients
NYHA class II and III heart failure
No recent MI (6 weeks)
No prior history of VT or VF
TWA, EF, SAECG, Mean RR, HRV,
NSVT, BRS tests performed
End-point Ventricular Tachyarrhythmic
Events (VT, VF or SCD)
Sensitivity 100%
PPV 21%

TKA: the only statistically significant predictor

![Graph showing survival rates for different TWA categories.](image)

**SCD TREATMENT & PREVENTION**

I) **IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD) THERAPY**

II) **ANTIARRHYTHMIC DRUG THERAPY**

III) **CATHETER ABLATION**

IV) **SURGERY**

**POST-MI SURVIVAL: LVEF & HRV INTERACTIONS**


**Survival in Congestive Heart Failure**

542 patients
EF =< 40%
NSR, no prior arrhythmias

Total number of subjects at risk:

<table>
<thead>
<tr>
<th>TWA-</th>
<th>TWA+</th>
<th>IND</th>
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<tr>
<td>181</td>
<td>161</td>
<td>195</td>
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<tr>
<td>83</td>
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<tr>
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<td>49</td>
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![Graph showing survival rates for different TWA categories.](image)

**AF TRANSFORMING TO VF IN A PATIENT WITH WPW SYNDROME**

![Graph showing AF transforming to VF.](image)
**WPW Syndrome: Disappearance of Ventricular Pre-excitation during RF Application**

**ANOMALOUS LEFT CORONARY ARTERY**

**EFFECTIVENESS OF BETTA BLOCKER THERAPY IN LQTS**

**PROBABILITY OF SUDDEN DEATH IN CHILDREN WITH LQTS: RELATION TO QTc**

**Primary Prevention vs. Secondary Salvage**

- Salvage rate for patients with sudden cardiac arrest is < 2%
- Therefore the major task is to identify patients at risk prior to the event
  - focus on primary prevention
  - identify and treat

**SCD: SECONDARY PREVENTION**
Treating survivors of out-of-hospital cardiac arrest with documented VT/VF

There are no controlled studies with placebo or no treatment arm

Randomized trials: Implantable Cardioverter/Defibrillator (ICD) vs Antiarrhythmic Drugs (AADs)

All randomized trials have shown that ICD therapy is superior to AAD (mostly amiodarone) therapy
AVID/CIDS/CASH Metanalysis

SCD: Difficulties with Primary Prevention

- Large numbers of patients at risk
  - need for simple, inexpensive, non-invasive testing
- Low incidence of sudden cardiac death among patients with known heart disease
  - post myocardial infarction mortality rates ~5%
  - 'needle in a haystack'

PVC Hypothesis:

CAST-I

Prognosis of Post-MI Patients Treated with Placebo vs. Encainide/Flecainide

SCD: PRIMARY PREVENTION

ANTIARRHYTHMIC DRUG (AAD) TRIALS

None of the many prospective, controlled, AAD trials, except for one, in high-risk patients (post-MI, CHF) showed any survival benefit with AAD

DETECTION & TERMINATION OF VT BY ICD

Ventricular Tachycardia  Sinus Rhythm

atrial electrogram  ventricular electrogram
SCD: PRIMARY PREVENTION
ICD THERAPY

- 4 randomized, prospective trials showed survival benefit with ICD in:
  - Ischaemic heart disease and non-sustained VT
  - Ischaemic heart disease and depressed LV function
  - CHF and depressed LV function (ischaemic or non-ischaemic)

- ICD-related survival benefit not established in:
  - Patients undergoing surgical coronary revascularization
  - Implantation immediately after acute MI

PRIMARY PREVENTION OF SCD
MADIT-II Survival Results


Efficacy of ICD for Prevention of Sudden Death in Patients with HCM
Retrospective Multicenter Study; n=128


Risk Profile & Treatment Algorithm in Brugada Syndrome

ICD Therapy in Repolarization Abnormalities:
Indications

Lots Presenting with Cardiac Arrest

Lots with Recurrent Syncope on Beta Blocker Rx
- Positive family Hx for Sudden Death
- Markedly prolonged QT at baseline

Idiopathic VF

Patients with Brugada Syndrome, who are symptomatic or have a positive family history and a positive response to PCS